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PATENT

Attorney Docket 9577-25

**IN THE UNITED STATES PATENT & TRADEMARK OFFICE**

Applicant: Isa Odidi and Amina Odidi :  
Serial No. 09/845,497 : Group Art Unit: 1616  
Filed: May 1, 2001 : Examiner: Alton N. Pryor  
For: Extended Release Pharmaceuticals

**DECLARATION UNDER 37 C.F.R. 1.132**

Box Fee Amendment  
Commissioner for Patents  
Washington, DC 20231

Isa Odidi and Amina Odidi declare that:

1. We are co-inventors of and are familiar with the present U.S. Patent Application Serial No. 09/845,497, and we are familiar with the several Official Actions issued with respect to the present application.
2. The claimed encasement coat comprises "one or more layers of a polymeric film encasing said capsule, tablet or pellet, said encasement coat being non-permeable and soluble in a pH of above about 5.0 and comprising about 5 up to less than 50% by weight polymer and about 0.5%-30% by weight plasticizer of polyethylene glycol".
3. On page 3 of the Office Action mailed August 4, 2008, the Examiner asserts that the "Applicant merely states without proof that an artisan would not consider using cellulose acetate in the encasement coat since cellulose acetate would dissolve and form a semi-permeable membrane at pH below 5. The Examiner argues that the claims are not limited to specific cellulose esters and that the Applicant does not support the cellulose dissolution statement with data." (emphasis added)
4. In order to demonstrate that cellulose acetate would dissolve at a pH below 5.0 and hydroxypropyl methyl cellulose phthalate would dissolve at a pH of above about 5.0, a

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percent release of pharmaceutical active was measured, over a period of 24 hours, at different pH's.

5. a) One batch of Carvedilol spheres (Carvedilol being the pharmaceutical active) was coated with hydroxypropyl methyl cellulose phthalate (an enteric cellulose ester) in a fluid bed coater. The coated spheres contain 20% wt/wt of hydroxypropyl methyl cellulose phthalate and 6% wt/wt of polyethylene glycol.

b) Another batch of Carvedilol spheres was coated with cellulose acetate (a non-enteric cellulose ester) in a fluid bed coater. The coated spheres contain 20% wt/wt of cellulose acetate and 6% wt/wt of polyethylene glycol.

6. Percent release was measured over 24 hours using an automated dissolution system (paddle speed set at 100 rpm and temperature of 37°C). U.S. Pharmacopoeia (USP) phosphate buffer at different pH (pH 1.5, pH 4.0, pH 5.0, pH 5.5, pH 6.0, pH 6.5 and pH 7.0) was used as the test fluid.

7. The results are shown in Figures 1 and 2 of Schedule A.

8. The results of Figures 1 and 2 show a marked pH dependency of drug release for the Carvedilol spheres coated with hydroxypropyl methyl cellulose phthalate. Drug release occurs when the pH is higher than about 5.0. This is representative of other cellulose esters such as cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate succinate, and cellulose acetate trimellitate. Methacrylic acid polymers also behave in the same way.

9. In contrast, the results of Figures 1 and 2 show drug release, and hence, permeability below pH 5 for cellulose acetate. In fact, the drug release falls as pH is increased from 1.5 to pH 7.0. No significant changes occur with cellulose acetate and no increase in drug release occurs when the pH is higher than 4.0.

10. The difference in drug release between pH 1.5 and pH 7.0 is about +90% for Carvedilol spheres coated with hydroxypropyl methyl cellulose phthalate. While the difference in drug release between pH 1.5 and pH 7.0 is about -10% for Carvedilol spheres coated with cellulose acetate.


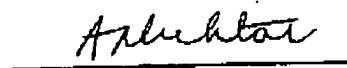
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11. The results indicate very clearly that hydroxypropyl methyl cellulose phthalate behaves much differently from cellulose acetate. Their mechanism of drug release is different. Hydroxypropyl methyl cellulose phthalate is very pH reactive while cellulose acetate is not. The results also show that cellulose acetate coated Carvediol spheres "leak" significantly (i.e. are permeable) at pH below about 5.0 while hydroxypropyl methyl cellulose phthalate coated Carvediol spheres do not.

12. These results show that cellulose acetate is not soluble above pH 5.0 and that hydroxypropyl methyl cellulose phthalate is soluble above pH of 5.0. Therefore, hydroxypropyl methyl cellulose phthalate is a suitable polymer for the encasement coating of the present application and cellulose acetate is clearly not a suitable polymer and one skilled in the art would not choose it since it would not satisfy the criteria of the claimed invention. The cellulose acetate does not dissolve any further past pH of 4.

13. We further declare that all statements made herein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

26<sup>th</sup> November, 2008  
Isa OdidiNovember 27<sup>th</sup>, 2008  
Amina Odidi